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Abstract:

Title of Thesis: Effects of Glycemic Control on Soft Tissue Wound Healing around Dental Implants for Patients with Type 2 Diabetes

Morgan Barker, Master of Science in Biomedical Science, 2019

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This study evaluated the effects of glycemic status on soft tissue wound healing following dental implant placement. A total of 164 edentulous patients with HbA1c levels up to 11.5% received two mandibular transmucosal dental implants. Patients' self-reported pain (VAS and # days with pain) and soft tissue healing (edema, erythema, exudate, oral pain, flap closure, infection, and hematoma) were evaluated one week after placement.

HbA1c and diabetes status were not significantly associated with any soft tissue healing complications. Pain_VAS was significantly correlated with Edema, Infection, Days in Pain and Oral Pain. Flap Closure was correlated with Oral Pain. Infection was correlated with Oral Pain and Days_Pain. Stepwise regression also identified HbA1c as significantly contributing to the VAS pain score.

The findings of this study clarify the low risk for post-surgical healing complications independent of poor glycemic control, extending the opportunities for dental implant therapy for patients with diabetes.

Effects of Glycemic Control on Soft Tissue Wound Healing around Dental Implants for Patients with Type 2 Diabetes

by
Morgan Barker Hurwitz

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Master of Science
2019

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I. INTRODUCTION

The process of wound healing is classically separated into a series of overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution. The phases of hemostasis and inflammation are often considered as one phase, with considerable overlap in the functions between phases (Gosain A, 2004) (Broughton G, 2006).

Hemostasis serves as the initiating step and begins immediately after wounding. Traumatic injury causes capillary damage and hemorrhage and, as a result, a blood clot is formed (Polimeni G, 2006). The clot and surrounding wound tissues release pro-inflammatory cytokines and growth factors such as TGF-B, PDGF, FGF and EGF as activated platelets degranulate. This clot also serves as a temporary shield protecting the denuded wound tissues and provides a provisional matrix over and through which cells can migrate during the repair process (Guo S, 2010) (Martin, 1997)

Once bleeding is controlled, inflammatory cells migrate into the wound (chemotaxis) and promote the inflammatory phase, which is characterized by the sequential infiltration of neutrophils, macrophages, and lymphocytes (Gosain A, 2004) (Broughton G, 2006). Neutrophils and monocytes are recruited from the circulating blood in response to molecular changes in the surface of endothelial cells lining capillaries at the wound site. Neutrophils normally begin arriving at the wound site within minutes of injury and act to clear invading bacteria and cellular debris as well as signaling to activate local fibroblasts and keratinocytes. These cells also produce substances, such as proteases and reactive oxygen species (ROS), which cause some additional bystander damage (Guo S, 2010). Macrophages continue to accumulate at the wound site and release growth factors and

cytokines that promote the inflammatory response by recruiting and activating additional leukocytes. These cells are also responsible for inducing and clearing apoptotic cells including neutrophils and any remaining pathogenic organisms and matrix debris. Macrophages stimulate keratinocytes, fibroblasts and angiogenesis to promote tissue regeneration, promoting the transition to the proliferative phase of healing (Guo S, 2010).

The proliferative phase extends from the inflammatory phase and is characterized by epithelial proliferation and migration over the provisional matrix within the wound (re-epithelialization). Fibroblasts and endothelial cells are the most prominent cell types present and support capillary growth, collagen formation, and the formation of granulation tissue at the site of injury. Fibroblasts responsible for the replacement of the provisional extracellular matrix produce a new collagen-rich matrix.

Following robust proliferation and extracellular matrix (ECM) synthesis, wound healing enters the final remodeling phase (Guo S, 2010). Some fibroblasts undergo transformation in myofibroblasts and express alpha-smooth muscle actin, which is responsible for wound contraction. Angiogenesis is accomplished through the migration of endothelial cells into the provisional wound matrix to form vascular tubes and loops and finally undergo apoptosis to reduce the number of vascular units once the provisional matrix matures. Epithelial cells from the basal layer proliferate and migrate through the fibrin clot and eventually the epithelium is sealed. Maturation of the granulation tissue will lead to regeneration or repair of the injured tissues (Polimeni G, 2006) (Martin, 1997).

The healing of wounds in non-oral sites has been studied in great detail (Clark, 1996). The general principles of healing, and the cellular and molecular events observed in non-

oral sites, also apply to the healing processes that take place following periodontal surgery (Polimeni G, 2006). Many of the cellular and molecular events in healing of periodontal wounds are similar to those seen in wounds elsewhere in the body with the added presence of a mineralized tissue interface with the epithelium and connective tissue in periodontal wounds (Aukhil, 2000).

Interruptions, aberrancies, or prolongation in any of these processes can lead to delayed wound healing or a non-healing chronic wound (Guo S, 2010). There are many factors that can affect wound healing which interfere with one or more phases in the process, thus causing improper or impaired tissue repair (Guo S, 2010). Local factors include supply of oxygen, infection and foreign body. Systemic factors include ageing, sex, stress, failure of circulation, obesity, medications, alcohol, smoking, immunosuppressed state, nutrition and many systemic diseases, such as diabetes.

Diabetes affects hundreds of millions of people worldwide with the potential for impairments in the healing of acute wounds well documented. The impaired healing that occurs in individuals with diabetes involves hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, high levels of metalloproteases, damage from ROS and AGEs, decreased host immune resistance, and neuropathy (Guo S, 2010). The decrease in vascular circulation with diabetes causes hypoxia leading to impaired wound healing due to the enhancement in the initial inflammatory reactions and increase in oxidant free radical. Elevations in oxidant free radicals are also induced by an increase in blood sugar level (Vincent AM, 2004) and promote advanced glycation end-products (AGE's) inhibiting vascularization (Hujiberts MS, 2008). Oxidant radical induces incomplete formation and distraction of gap

junctions of blood vessels, while elevated blood-sugar levels directly cause incomplete formation of gap junctions and promotes the production of TNF-alpha involved in inhibition of hemangiogenesis (Abiko Y, 2010).

Diabetic patients may be under a state of immunosuppression related to the dysfunction of neutrophils, monocytes, and several types of antimicrobial peptides, elevating their susceptibility to infection (Abiko Y, 2010). Diabetes mellitus is generally indicated as a risk factor for the infection of a variety of implants such as prosthetic joints, pacemakers, implantable cardioverter defibrillators, penile implants, and urinary catheters. Although implantable medical devices are considered biocompatible by the Food and Drug Administration, the adverse tissue healing that occurs adjacent to these foreign objects is a leading cause of their failure. The foreign body response leads to fibrosis, encapsulation of the device, and a reduction or cessation of device performance (Le, 2011).

The physiologic factors that influence wound healing and infection associated with biomedical implants and devices has been studies through the use of animal models. In a diabetes-induced rat model using streptozotocin (STZ), four inflammatory parameters: myeloperoxidase activity (MPO), NAG, and two cytokines, TNF-alpha and monocyte chemotactic protein-1 (MCP-1) levels were measured after insertion of a subcutaneous implant. All parameters, except for NAG activity (macrophage activation), were higher in implants from diabetic rats when compared with those from non-diabetic animals. All fibrogenic markers (TGF-B1, collagen deposition, fibrous capsule thickness, and foreign body giant cells) decreased under diabetic conditions, whereas apoptosis increased. Overall, this study showed that fibrous capsule formation and presence of

foreign body giant cells were attenuated in the hyperglycemic environment (Oviedo-Socarras, 2014).

Streptozotocin-induced models for diabetic wound healing have revealed delays in the wound-healing process as a characteristic of the hyperglycemic state. Histological reports in streptozotocin-induced Wistar rats after a standardized laceration injury showed delayed wound healing patterns in diabetic rats through 10 days when compared to controls. In addition, inflammation and polymorphonuclear cell counts were consistently higher in diabetic rats (Alzoubi F, 2017). Similarly, in a longer study of 21-days, there was a delay in fibroblastic proliferation into the area of healing in the wounds of diabetic rats with an increased acute inflammatory response during the course of the wound healing process after tongue ulceration when compared to non-diabetic controls. However, the healing process was essentially the same at 21 days in both the experimental and the control groups of these animals (Abbey L, 1973).

Patients with diabetes mellitus are thought to have a high risk of postoperative complications, including infections, impaired wound healing, cardiovascular events, venous thromboembolism and mortality (Visser, 2015). However, a recent review of studies evaluating the association between HbA1c levels in patients with diabetes and post-operative complications could not find sufficient evidence to conclude that higher HbA1c levels in patients with diabetes are predictive of postoperative complications, particularly for joint replacement surgeries. Importantly, the consideration to delay or prevent patients lacking good control from having these procedure may in fact promote worsening hyperglycemia by compromising lifestyle management, which is the first and most effect step in achieving diabetes control (Lopez LF, 2017).

It has been suggested that optimizing a patient's intra-operative glycemic control may reduce post-operative infections in non-cardiac surgery patients. In a study evaluating 1100 patients undergoing non-emergency procedures across all surgical subspecialties, pre-operative glycosylated hemoglobin (HbA1c) level associations with post-operative infections were assessed. Results showed that patients with HbA1c <6.5% and those with HbA1c >= 6.5% showed no statistically significant difference in overall infection rate. Both linear regression and multivariate analysis failed to identify HbA1c as an individual predictor of infection. However, elevated HbA1c was predictive of significantly increased risk of post-operative infection when associated with increased age (>= 81 years of age) or 'dirty' wounds. This study shows that risk factors of post-operative infectious complication are multi-factorial, likely synergistic, and appear to affect some patient populations differently (Blankush, 2016).

Diabetic patients are also thought to be at an increased susceptibility to periodontal diseases and oral infection (Abiko Y, 2010). Oral soft tissue diseases such as angular cheilitis, apthous ulcers, candidiasis, tongue papilla atrophy and denture stomatitis were found to be more prevalent for diabetic individuals compared to their non-diabetic counterparts in a cross-sectional study evaluating 405 adult subjects with diabetes and 268 control subjects without diabetes (Guggenheimer J, 2000). Further complicating circulation and vascularization impairments, diabetic patients suffer from hypofunction of the salivary gland leading to lower level of scavengers, higher level of free radicals, reduced anti-microbial peptides and proteins leading to more oxidative stress causing the protracted wound healing in diabetes (Bernardi MJ, 2007) (Abiko Y, 2010). There is also a higher concentration of MMP-8, a type of collagenase, detected in saliva of diabetic

individuals that contributes to the degradation of extracellular matrices and impairing wound healing (Costa, 2010) (Collin HL, 2000). Epidermal growth factor (EGF) functions in cell growth and differentiation in oral tissue and promotes re-epithelialization of oral mucosa. EGF is decreased in the saliva of diabetics, which may also contribute to the protracted wound healing on oral mucosa in diabetic individuals (Barrientos, 2008).

Multiple studies have evaluated the effects of type 2 diabetes on the healing of dental extraction sockets. Power et al determined that well controlled diabetic patients tend to heal well following dental extractions by evaluating 56 insulin-dependent diabetic patients and 49 non-diabetic patients undergoing an extraction. The results revealed seven patients (12.5%) in the study group showed delayed healing following extraction, while only four patients (8.2%) in the control group suffered delayed healing; however, the findings were not statistically significant (Power DJ, 2019). Similarly, 224 Type 2 diabetic patients taking oral hypoglycemics and 232 non-diabetic individuals were evaluated after undergoing a dental extraction and followed for four weeks. Blood glucose levels were drawn from each patient right after local anesthetic and prior to extraction. The results revealed 28 patients had delayed healing beyond one week, 12 in diabetic group and 16 in the non-diabetic group, showing no statistically significant difference in post-extraction outcome between Type 2 diabetic patients on oral hypoglycemics and the control group. All patients had fully healed within four weeks (Huang S, 2013). Fernandes et al also showed that type 2 diabetes or glycemic control is not a risk factor for experiencing postoperative complications in people undergoing dental extractions. This study evaluated 53 participants with type 2 diabetes and 29

participants without over 60 days after surgery and the findings suggest that although people with type 2 diabetes may have impaired neutrophil function; there was no association with an increased risk of experiencing postoperative complications (Fernandes KS, 2015). Taken together, these studies suggest that while there may be some minor delays in oral surgical healing in patients with diabetes, there does not appear to be clinically important compromises in the wound healing responses. Furthermore, as these studies focused on relatively well-controlled patients, they do not clarify the role of glycemic control in the healing response.

There have been several studies assessing the relationship between diabetes and glycemic control and implant success or failure. Both human and animal studies have shown that poorly controlled diabetes negatively affects peri-implant bone formation and bone mineralization (Von Wilmowsky C, 2011) (Oates T., 2009). It was demonstrated in humans that alterations in implant stability were consistent with impaired implant integration for persons with type 2 diabetes mellitus in direct relation to hyperglycemic conditions. Persons with HbA1c >= 8.1% had a greater maximum decrease in stability from baseline and required approximately twice the time for healing (Oates T., 2009). However, clinical survival outcomes were not affected within the clinical protocols employed in the study. In diabetic pigs, pathological changes were visible in the skin vasculature after 6 months, with significant arterial wall thickening in the diabetic group. The bone-implant contact as well as the peri-implant bone mineral density was also significantly reduced in the diabetic group after 4 and 12 weeks (Von Wilmowsky C, 2011). Another clinical study found implant survival rates after one year of loading for patients with HbA1c levels up to 11.5% at baseline and as high as 13.3% over one year

were 99.0%, 98.9% and 100%, respectively for patients who did not have diabetes, those with well-controlled diabetes and those with poorly controlled diabetes. This study supported earlier findings (Oates T., 2009) showing that early bone healing and implant stability were altered; however, elevated HbA1c levels were not associated with altered implant stability after one year of loading (Oates T, 2014). Similarly, peri-implant fluid evaluation demonstrated that poor glycemic status negatively influenced the profile of local bone markers over 12 months; however, dental implant stability when assessed over 12 months does not seem to be influenced by glycemic control (Ghiraldini B, 2016). These studies highlight a tendency toward lower implant stability with hyperglycemia during the initial healing phases, but minimal effects over longer periods of time.

In addition to studying general surgical complications in the diabetic patients, recent studies have evaluated the impact of diabetes on dental implant integration. However, looking across available studies, the role for hyperglycemia or elevated HbA1c levels has only limited assessments relative to the development of intraoral surgical post-operative complications. Furthermore, the few studies available have made these determinations based on patients having moderate glycemic control, and not explored the effects of poor glycemic control. Currently, there is no evidence regarding oral soft tissue healing for patients with high HbA1c levels, nor for soft tissue healing associated with dental implant placement. Therefore, the goal of this study is to evaluate early (one week) soft tissue wound healing following dental implant placement in patients with diabetes mellitus with HbA1c levels approaching 12%.

II. METHODS

A. Participant Enrollment

This single-center, prospective, clinical cohort study was performed at the School of Dentistry, University of Texas Health San Antonio (UTHSCSA) with the goal to determine the effects of glycemic control on implant related outcomes in patients with mandibular implant supported complete over-dentures.

1. Inclusion criteria

Patients needed to meet the following inclusion criteria: age ≥25 years; patient had clinically acceptable complete dentures for ≥6 months; ridge width in anterior mandible to support 4.1 mm diameter implants with a length of 8, 10, or 12 mm. Participants were included who did not have diabetes, and had an HbA1c level that was less than 5.9 percent or a fasting blood glucose level that was 100 mg/dL or lower. The study utilized a single Clinical Laboratory Improvement Amendments– certified commercial laboratory to measure HbA1c values. Medical management of diabetes by means of diet, oral hypoglycemic agents, insulin or combination therapy was allowed. Patient's height, weight, waist circumference, and blood pressures were also recorded. Venous blood was drawn at the enrollment appointment to obtain HbA1c levels for classification as follows: non-diabetic (ND; HbA1c ≤ 5.9%), well-controlled type 2 diabetic (WCD; 6% ≤ HbA1c ≤ 8%), poorly controlled type 2 diabetic (PCD; HbA1c ≥ 8.1%).

2. Exclusion criteria

Criteria for exclusion from the study included pregnancy, systemic conditions other than diabetes that are considered contraindications to surgery or implant therapy, viral or autoimmune disease, reported use of antiresorptive drugs, reported

drug/alcohol abuse, reported smoking habit, untreated oral infection(s), autogenic or allogeneic bone grafting at implant site(s) that was done within 1 year of the study, alloplastic bone grafting at implant site(s), and HbA1c >12% at enrollment.

B. Implant Surgery

Implant surgery was carried out by multiple clinicians under the supervision of the principal investigator following standard surgical protocols. All patients received two transmucosal dental implants (4.1 mm in diameter and 8, 10 or 12 mm in length, SLActive, Straumann, Basel, Switzerland) at the site of the mandibular incisors or canines. Implant length was determined at the time of the surgery by the surgeon, with the same length implants placed in both sites. After implant placement, transmucosal healing caps were placed and the denture base was adjusted to eliminate any contact with the implants. The implants were restored with two locator attachments after a four-month healing period.

C. Post-operative Protocol

All patients were given post-operative prescriptions for amoxicillin 500 mg or clindamycin 150 mg, to be taken three times a day for seven days and 0.12% chlorhexidine gluconate mouth rinse, to be used for 30 seconds twice a day for two weeks. The patients were seen for post-operative visits at weeks 1, 2, 3, 4, 6, 8, 10, 12 and 16, with restoration occurring at 16 weeks.

D. Data Collection

Two calibrated examiners who were masked to the diabetic and glycemic status of the patients measured all implant-related outcomes. Three groups were determined based on their HbA1c values: Non-Diabetes (<6%), well-controlled Diabetes (>6% and <8%) or poorly controlled Diabetes (>9%). Implants were assessed over a four-month healing period after placement and prior to implant restoration. Implant survival was defined as implants lacking peri-implant radiolucency, signs of clinical mobility, pain or any other signs of failure of the implant to integrate at four months facilitating removal of the implant (Albrektsson T, 1986). Investigators assessed implant-related biological complications at each study visit. These complications included any sign of infection such as pain, swelling or exudate that did not require removal of the implant, but may have been sufficient to warrant antibiotic or other therapeutic intervention or change in clinical management procedures.

This report focuses on the first week post-operative data and evaluates the soft tissue healing around the dental implants. The examiners analyzed and reported the severity of edema, erythema, exudate, oral pain, flap closure, infection and/or hematoma on a scale of none (0), slight (1), moderate (2), or severe (3) in the patient's chart. A score of mild (1) was defined as evident to the examiner but the patient was unaware of the condition (did not interfere with routine activity), and no additional treatment required. Moderate (2) was defined as the patient being aware of the condition (or had some alteration in routine activity due to the condition), and no additional treatment required. Severe (3) was defined as patient awareness or altering

the patient's routine activities altered, and additional treatment was required to manage the condition.

Pre-surgical HbA1c levels were determined within two weeks of implant surgery (baseline) for each participant with subsequent assessments of HbA1c occurring at weeks 8 and 16 following surgery. Baseline HbA1c values were assessed relative to post-surgical healing for this investigation. The patients recorded their pain level at the first week post-operative appointment on a VAS scale, which was then measured in millimeters (0-100mm) and recorded. Patient's medications were also categorized.

E. Statistical Analysis

Statistical software used for analysis was JASP 0.9.2. Multivariate linear regression, Spearman's Rho correlation, and ANOVA were used to address two main questions, 1) the influence of clinical factors identified after one week on post-surgical pain using the patient reported pain level with a visual analog scale (VAS) as the dependent variable.; and 2) the influence of HbA1c levels (%) using the clinical healing parameters of edema, erythema, exudate, oral pain at one week, flap closure, infection and hematoma as dependent variables. Stepwise linear regression model was developed to characterize the predictive nature of HbA1c and the wound healing factors edema, erythema, exudate, oral pain at one week, flap closure, infection, and hematoma factors on the VAS pain score.

III. RESULTS

A total of 164 patients participated in the study. Patients receiving surgical placement of two mandibular anterior dental implants to provide overdenture support were evaluated at one-week post operatively for soft tissue wound healing, specifically healing factors of edema, erythema, exudate, oral pain at one week, infection, flap closure and hematoma. Of those patients, 47% were male and 53% were female. There was no statistically significant difference amongst the three groups in regards to gender. The age of study participants ranged from 38 to 85 years of age, with a mean age of 64 years with no statistically significant difference between non-, well-, or poorly controlled diabetic patients. There were statistically significant differences found among the three cohorts for glycemic status with regards to race, with Hispanic patients representing 64% of poorly controlled patients, 56% of well-controlled patients, and only 21% of non-diabetic patients. There was a statistically significant difference between non- and well-controlled diabetic patients and between non- and poorly controlled diabetic patients, but not one between well and poorly controlled diabetic patients. BMI was calculated for each patient revealing a mean BMI of 33.8 ($\pm$ 7.3). BMI was statistically different between the non-diabetic group and the well-controlled diabetic group and between the non-diabetic group and poorly controlled diabetic group; however, it was not statistically different between well and poorly controlled diabetic groups. There were no statistically significant differences between the systolic and diastolic blood pressures amongst the overall population. However, there was a statistically significant difference between non-diabetic patients and well-controlled diabetic patients for diastolic blood pressure. There was a statistically significant difference in the overall population in regards to pulse. Pulse was

statistically different between non- and poorly controlled diabetic patients and between well and poorly controlled diabetic patients; however there was no statistically significant difference between non- and well-controlled diabetic patients.

The overall mean HbA1c for the study patients was 6.9% with a range of 5% to 11.5% (see Table 2). Patient glycemic levels correlated strongly ($p<0.001$) with Diabetes Status groupings as shown in Figure 1.

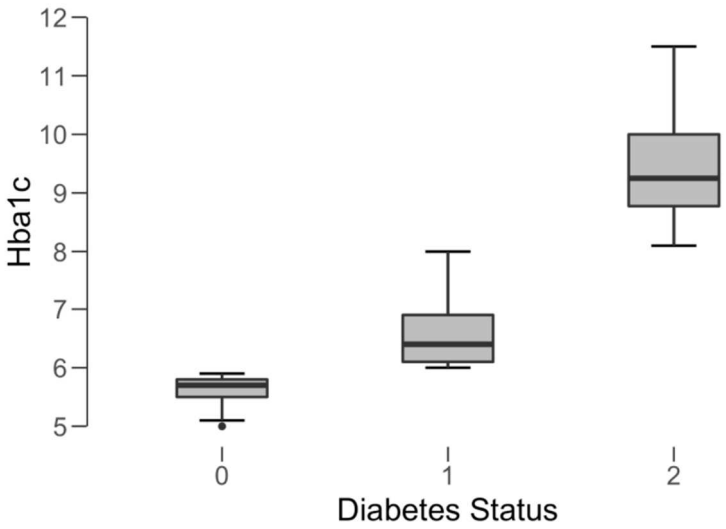

Figure 1: Glycemic Levels (% HbA1c) relative to Diabetes Status (None, Well-controlled, Poorly-controlled)

Table 1a shows the demographic information summarized with percentages and/or frequency of the population. Table 1 b shows the demographic information summarized with averages.

Variable	Level of Diabetes Control (HbA1c %)			Total	P value
	<6.0	6.0 – 8.0	8.0-12.0		
Gender	*n=56*	*n=72*	*n=36*	*n=164*	0.541
Male	28 (50)	35 (48.6)	14 (38.9)	77 (47)	
Female	28 (50	37 (51.4)	22 (61.1)	87 (53)	
Race	*n=56*	*n=71*	*n=35*	*n=162*	<0.001
White	41 (73.2)	28 (39.4)	11 (30.6)	80 (49.1)	
Black	1 (1.8)	1 (1.4)	1 (2.8)	3 (1.8)	
Asian	2 (3.6)	2 (2.8)	0 (0)	4 (2.5)	
Hispanic	12 (21.4)	40 (56.3)	23 (63.9)	75 (46)	

Table 1a. Summary of demographics (n (%))

Variable	Level of Diabetes Control (HbA1c %)			Total	P value
	<6.0	6.0 – 8.0	8.0-12.0		
BMI	28.9 (6.6)	32.9 (7)	33.8 (7.3)	31.8 (7.2)	<0.001
Age	64.6 (9)	65 (9.1)	61.6 (9.7)	64.1 (9.2)	0.17
Diastolic BP	83.3 (9.8)	78.1 (16.6)	80.8 (14.3)	80.5 (14.2)	0.12
Systolic BP	145.3 (19.3)	142.3 (21.1)	145.7 (20.1)	144.1 (20.2)	0.62
Pulse	71.4 (12.6)	74 (14.1)	79.3 (16.4)		0.03

Table 1b. Summary of demographics (Mean, (SD))

All patient's medications were categorized and compared using both the number of patients (Figure 2) and percentage of patients (Figure 3) amongst the total population.

The majority of patients were taking Heart/Circulatory medications (177 patients, 77%), followed by CNS/pain relief (116, 71%) and finally Diabetes medications (114 patients, 70%). The least used medications amongst the population were cancer drugs and anti-infective drugs with 3 patients (2%) and 5 patients (3%) respectively.

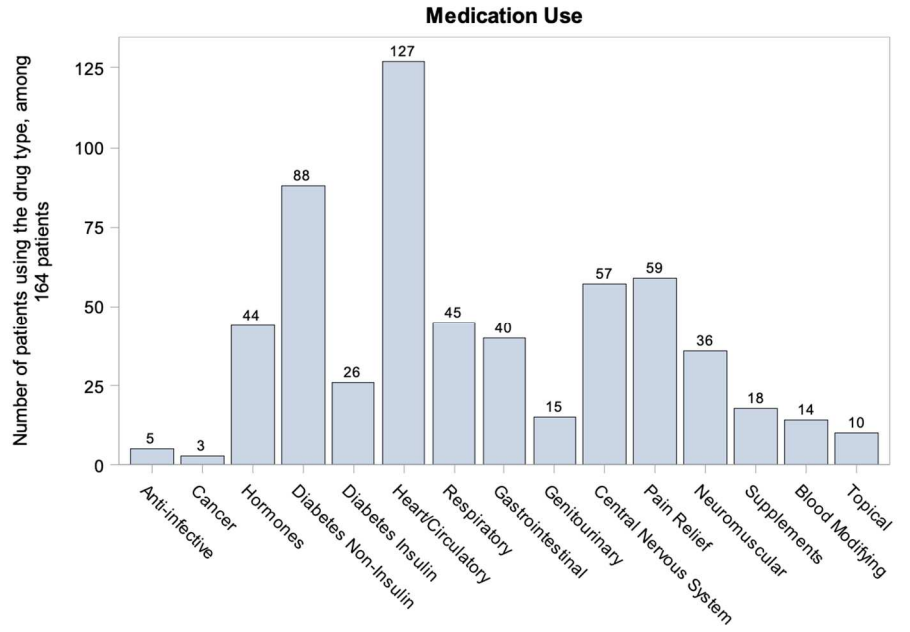

Figure 2. Number of patients using Medication category

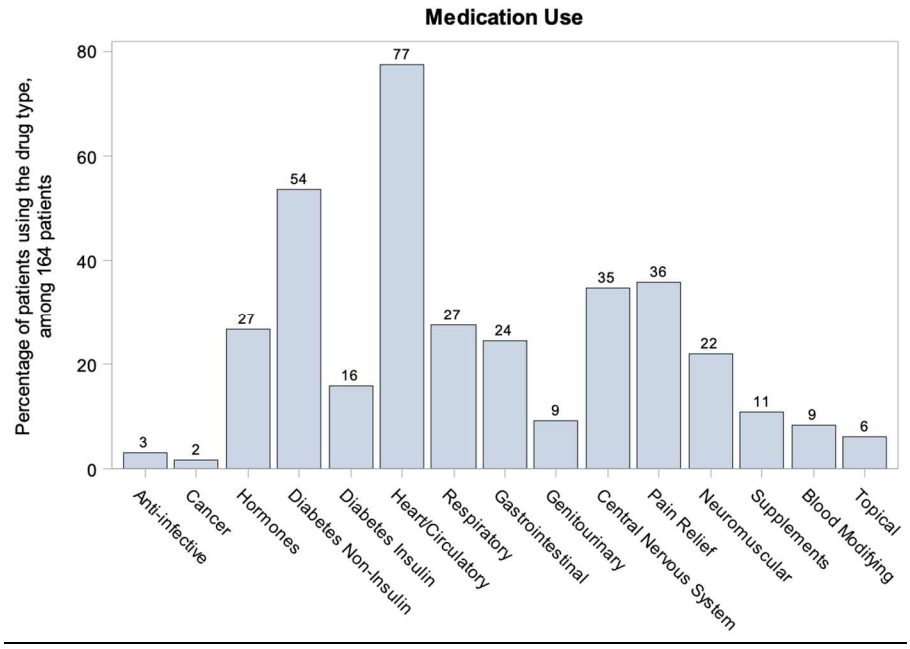

Figure 3. Percentage of patients using Medication category

Assessment of diabetes status on wound healing included effects on post-operative pain, with several outcome measures assessed, and clinical findings such as edema, erythema, exudate, hematoma, flap closure, and infection (Table 2). The mean HbA1c in the population was 6.9% with a range between 5-11.5%. The average pain VAS score was 35.8mm, with a range from 0-100, but the most common score being 0. The mode for days of pain was 2; however, the max range was 14. The median and mode for edema and erythema was 1, with a max range of 2. Exudate, oral pain at one week, flap closure and hematoma all had a median and mode of 0. These factors were independently correlated to the patient's reported level of pain at one week using a visual analog scale.

	HbA1c	Pain VAS	Days of Pain	Edema	Erythema	Exudate	Oral Pain at one week	Flap Closure	Infection	Hematoma
Mean	**6.9**	**35.8**	**3.4**	**0.91**	**0.89**	**0.05**	**0.58**	**0.40**	**0.02**	**0.15**
Median	**6.2**	**29**	**2**	**1**	**1**	**0**	**0**	**0**	**0**	**0**
Mode	**5.8**	**0**	**2**	**1**	**1**	**0**	**0**	**0**	**0**	**0**
Range Min	**5**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Range Max	**11.5**	**100**	**14**	**2**	**2**	**2**	**3**	**2**	**1**	**3**

Table 2: Descriptive Statistics for Wound Healing Factors

Correlation analyses across wound healing, pain; diabetes factors identified several significant relationships of interest (see Table 3). HbA1c levels correlated with the peri-operative blood glucose levels at the time of surgery (CBG_SX: rho=0.621;p<0.001). CBG_SX had a slight negative correlation with oral pain_1 week (rho=-0.184; p=0.041). Several factors were related to Pain_VAS, including Edema, Infection, and the other pain measures, Days in Pain and oral Pain at 1 week. There was no significant correlation between clinical findings of Erythema, Exudate, Hematoma, and compromised Flap Closure with Pain_VAS. Flap Closure was correlated with Edema, Erythema, and Oral Pain at 1 week, Infection, and Hematoma. Infection was correlated with Edema, Erythema, Hematoma, Pain_VAS, Oral Pain at 1 week, and Days_Pain,

		Hba1c	Diabetes Status	CBG_SX	Pain_VAS	Days_Pain	Edema	Erythema	Exudate	OralPain_1week	Flap Closure	Infection
Diabetes Status	Spearman's rho	0.931 ***	—									
	p-value	< .001	—									
CBG_SX	Spearman's rho	0.621 ***	0.607 ***	—								
	p-value	< .001	< .001	—								
Pain_VAS	Spearman's rho	0.098	0.091	0.066	—							
	p-value	0.210	0.245	0.460	—							
Days_Pain	Spearman's rho	0.023	0.048	-0.057	0.586 ***	—						
	p-value	0.777	0.543	0.527	< .001	—						
Edema	Spearman's rho	-0.046	-0.037	-0.010	0.241 **	0.136	—					
	p-value	0.560	0.636	0.911	0.002	0.086	—					
Erythema	Spearman's rho	-0.075	-0.076	-0.027	0.149	-0.008	0.425 ***	—				
	p-value	0.339	0.335	0.761	0.058	0.916	< .001	—				
Exudate	Spearman's rho	0.114	0.194 *	0.171	0.087	-0.013	0.163 *	0.135	—			
	p-value	0.148	0.013	0.058	0.273	0.873	0.038	0.088	—			
OralPain_1week	Spearman's rho	-0.100	-0.095	-0.184 *	0.377 ***	0.473 ***	0.194 *	0.116	0.125	—		
	p-value	0.206	0.228	0.041	< .001	< .001	0.013	0.143	0.113	—		
Flap Closure	Spearman's rho	-0.089	-0.083	-0.043	0.101	0.119	0.260 ***	0.171 *	0.063	0.283 ***	—	
	p-value	0.262	0.292	0.635	0.200	0.136	< .001	0.030	0.424	< .001	—	
Infection	Spearman's rho	-0.043	-0.033	-0.067	0.179 *	0.173 *	0.141	0.158 *	0.161 *	0.269 ***	0.257 ***	—
	p-value	0.587	0.677	0.457	0.023	0.030	0.073	0.045	0.041	< .001	< .001	—
Hematoma	Spearman's rho	-0.003	-0.020	0.030	-0.003	0.011	0.141	0.129	0.017	0.088	0.182 *	0.431 ***
	p-value	0.970	0.798	0.738	0.969	0.895	0.074	0.102	0.827	0.265	0.021	< .001

Table 3: Correlations between Wound Healing, Diabetes, and Pain Factors

Stepwise linear regression analysis of these factors developed a 4-step model predictive of the patients' self-reported pain using the Pain_VAS scores. Table 4 outlines the development of the stepwise linear regression model. Interestingly, HbA1c was identified

as a significant predictive variable impacting the Pain_VAS score. Table 4 reflects the model summary and can be interpreted using R^2 for the goodness of fit. The R^2 value for model 4 is 0.321, which is the highest value amongst the 4 models (Table 5). According to Model 4, for Days of Pain (0-7days), there were 4.048mm of increase on the VAS scale for each added day of pain the patient experienced. The oral pain at one week increased the VAS score 8 units for every increase from none, slight, moderate, to severe. For each shift in severity in edema, the patient's VAS score increased by 6.815mm. For every 1% increase in the patient's HbA1c score, there was a 2.667mm increase in the VAS score. However, there was no significant relationship (p=0.136) identified with Pain_VAS across the three diabetes status groups (Figure 4).

Coefficients

Model		Unstandardized	Standard Error	Standardized	t	p
1	(Intercept)	17.680	3.198		5.528	< .001
	Days_Pain	5.310	0.734	0.501	7.235	< .001
2	(Intercept)	16.271	3.189		5.102	< .001
	Days_Pain	4.278	0.824	0.404	5.192	< .001
	OralPain_1week	8.195	3.173	0.201	2.583	0.011
3	(Intercept)	10.877	4.092		2.658	0.009
	Days_Pain	4.300	0.816	0.406	5.272	< .001
	OralPain_1week	7.035	3.189	0.172	2.206	0.029
	Edema	6.507	3.144	0.142	2.070	0.040
4	(Intercept)	−7.598	9.807		−0.775	0.440
	Days_Pain	4.048	0.816	0.382	4.960	< .001
	OralPain_1week	8.042	3.193	0.197	2.518	0.013
	Edema	6.815	3.114	0.149	2.188	0.030
	Hba1c	2.667	1.289	0.140	2.068	0.040

Table 4. Stepwise Linear Regression model for factors affecting VAS pain score

Model Summary

Model	R	R^2	Adjusted R^2	RMSE
1	0.501	0.251	0.246	25.60
2	0.531	0.282	0.273	25.14
3	0.549	0.302	0.288	24.88
4	0.566	0.321	0.303	24.62

Table 5: Model Summary for factors affecting VAS pain score

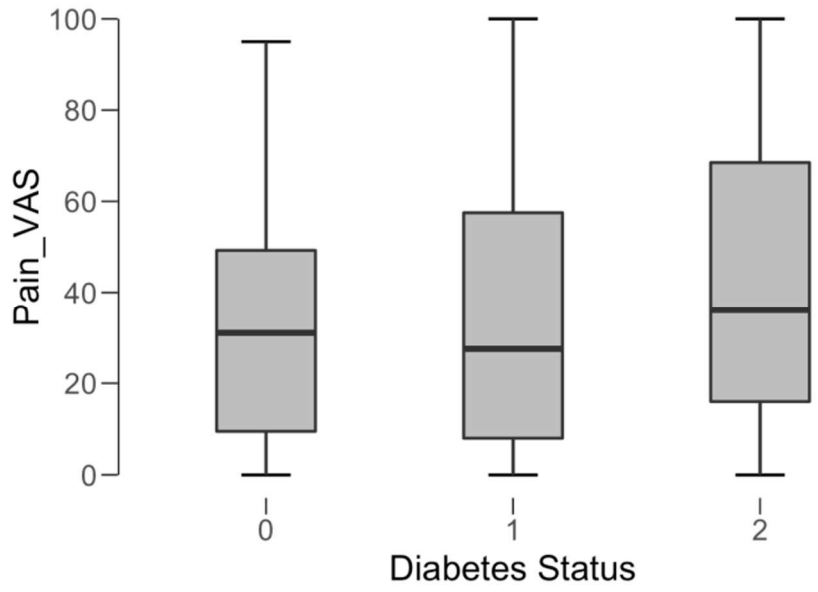

Figure 4: Box Plot of Relationship between Diabetes Status and Pain_VAS. There was no significant relationship (p=0.136) identified across these groups.

In evaluating the role of glycemic levels to influence post-surgical healing, it was found HbA1c level did not correlate with any wound healing/infection factors (Table 5), Similarly, the categorical classification of Diabetes Status did not have a significant positive correlation with any healing/infection factors (Table 6).

Clinical Outcomes		HbA1c Category				
	Level	*None*	*Well controlled*	*Poorly controlled*	*Total*	*P value*
Erythema	0	9 (16.4)	18 (25)	11 (30.6)	38 (23.3)	0.33
	1	40 (72.7)	44 (61.1)	20 (55.6)	104 (63.8)	
	2	6 (10.9)	10 (13.9)	5 (13.9)	21 (12.9)	
Edema	0	13 (23.6)	17 (23.6)	12 (33.3)	42 (25.8)	0.63
	1	32 (58.2)	45 (62.5)	16 (44.4)	93 (57.1)	
	2	10 (18.2)	10 (13.9)	8 (22.2)	28 (17.2)	
Days of Pain	> 2	28 (50.9)	30 (43.5)	21 (58.3)	79 (49.4)	0.33
	≤ 2	27 (49.1)	39 (56.5)	15 (41.7)	81 (50.6)	
Flap Closure	Yes	19 (35.2)	20 (27.8)	8 (22.2)	47 (29)	0.43
	No	35 (64.8)	52 (72.2)	28 (77.8)	115 (71)	
Oral Pain 1 week	Yes	28 (51.9)	32 (44.4)	13 (36.1)	73 (45.1)	0.35
	No	26 (48.1)	40 (55.6)	23 (63.9)	89 (54.9)	

Table 6. Analysis for Effects of Diabetes Status on Wound Healing Outcomes. All other outcomes (Exudate, Infection, Hematoma) showed no association due to minimal events.

IV. DISCUSSION

With hundreds of thousands of implants being placed each year in the United States, it is important to consider the patient population that is receiving endosseous dental implants. At present, there are no reports of absolute medical contraindications for implant placement, but relative contraindications do exist (Cochran, 1996). Poor glycemic control has been considered a relative contraindication to implant therapy and with 12-14% of the United States adult population with diabetes (Menke A., 2015), it is crucial we understand our limitations or lack thereof, in this patient population. Several patients with diabetes have difficulty maintaining their glycemic control for a variety of reasons despite pharmacological therapy, which could potentially prevent them from receiving dental implant therapy. These compromises in function could significantly affect their overall dietary management due to masticatory dysfunction, possibly worsening a cycle of poor glycemic control (Oates T, 2014).

These considerations are significant findings in light of the recent debate over raising the target HbA1c level for adult patients with type 2 diabetes. The American Diabetes Association (ADA) recommends a target A1c of less than 7% for non-pregnant adult diabetic patients. In contrast, the American College of Physicians (ACP) has shifted their target from less than 7% to a range between 7-8% due to evidence from several large, long-term randomized control trials showing that aggressive pharmaceutical therapy increases both side effects and costs. In fact, hypoglycemic events were found to be more severe in the intensive treatment groups aimed at improving overall glycemic control and intensive treatment did not reduce the risk for major adverse cardiovascular events, stroke, congestive heart failure or major microvascular events (Qaseem A, 2018).

It is important to consider that the ACP is recommending a higher target HbA1c because reducing glycemic control is not necessarily reducing the overall risks in patients, similar to what we have found in our study.

With these recent changes in guidelines for the management of glycemic levels in patients with diabetes focus more on the risks associated with hypoglycemia than those associated with hyperglycemia. These changes elevating the therapeutic targets of HbA1 raise importance of this study, as more dental implant patients may be seen with what is considered poor glycemic control. Viewing elevated glycemic levels as a contraindication may undermine the overall wellbeing of the patient and deny them optimal dental care.

To thoroughly examine the role of glycemic status as a contraindication to dental implant therapy, we have addressed this issue systematically by focusing individually on short-term healing associated with the surgical placement of implants as reported in this paper, the potential for implant integration to occur for patients with HbA1c levels over 10%, and longer term complications that may be impacted by metabolic compromises in association with the implant environment.

This study failed to identify clinically important post-surgical complications following dental implants placement in diabetic patients in relation to glycemic control. Evaluating glycemic status as a continuous variable using HbA1c percentages failed to identify a significant correlation with any post-surgical complication. Interestingly, on further examination using stepwise regression, HbA1c levels did contribute significantly as a predictor variable in the pain score.

Amongst the total population of 164 patients, there was no statistically significant difference amongst the three groups, non-, well, or poorly controlled diabetes, in regards to gender or age. There were statistically significant differences found among the three cohorts for glycemic status with regards to race, with Hispanic patients representing 64% of poorly controlled patients, 56% of well-controlled patients, and only 21% of non-diabetic patients. There was a statistically significant difference between non- and well-controlled diabetic patients and between non- and poorly controlled diabetic patients, but not one between well and poorly controlled diabetic patients. This finding is consistent with previous studies showing a higher prevalence of diabetes in the Hispanic population (Menke A., 2015); however, the total number of non-Hispanic black diabetic patients was lower in our population compared to the NHANES data, which is most likely a result from the limited number of non-Hispanic black participants in the overall study population. This discrepancy in the limited number of non-Hispanic black and non-Hispanic Asians in the study may limit applicability within the general population.

BMI was calculated for each patient, as it is well documented that obesity is correlated with the development of type 2 diabetes. The mean BMI for this study was 33.8. When analyzed, BMI was shown to be significantly different between the non-diabetic group and the well-controlled diabetic group and between the non-diabetic group and poorly controlled diabetic group, as expected for this disease condition. BMI was not shown to be significantly different between well and poorly controlled diabetic groups. This association between obesity and glycemic control is consistent with the literature that there is a positive and statistically significant association between being overweight or obese and having suboptimal glycemic control (Bae JP, 2016) (Huh JH, 2014).

Glycemic control in Diabetes has also been linked to cardiovascular disease. Cardiovascular disease is the major cause of death in patients with type 2 diabetes, as more than 60% of these patients die of myocardial infarction or stroke, and an even greater proportion of patients have serious burdensome complications (Fox CS, 2007). Although epidemiological evidence exists in favor of an adverse role of poor glucose control on cardiovascular events, intervention trials have been less conclusive (Giorgino F, 2013). The literature relates to our evaluation of the medications in our patient population, with 77% of the patients taking heart/circulatory medications, which is the highest percentage of all medications considered. There were no statistically significant differences between the systolic and diastolic blood pressures amongst the overall population. This could be due to the high number of patients taking cardiovascular-type medications and being well controlled. However, there was a statistically significant difference between non-diabetic patients and well-controlled diabetic patients for diastolic blood pressure. There was a statistically significant difference in the overall population in regards to pulse. Pulse was statistically different between non- and poorly controlled diabetic patients and between well and poorly controlled diabetic patients; however there was no statistically significant difference between non- and well-controlled diabetic patients.

There is limited research on the prevalence of pain and its association with glycemic control, especially in regards to dental implant post-operative pain. Prevalence of pain and the association with quality of life, depression and glycemic control in patients with diabetes has been evaluated in a cross sectional, multi-site, prospective cohort study and found that moderate to extreme pain was present in 57.8% of diabetic

patients. This study evaluated both acute and chronic pain as well as neuropathic and/or non-neuropathic painful conditions. This study is supportive of our patient population with 71% (116 patients) taking general pain relief medications or medications for central nervous system relief. Pain was strongly associated with poorer mental health and physical functioning, but not worse glycemic control (Bair MJ, 2010). Specifically, chronic pain was evaluated in 993 patients with diabetes and revealed that chronic pain and greater pain severity were both associated with poorer overall diabetes self-management and increased difficulty with certain self-care activities, such as exercising on a regular basis (Krein SL, 2005). Consistent with our findings, a significant independent relationship between pain and HbA1c was found in a predominantly black population where participants reporting pain were more than twice as likely to have HbA1c levels greater than 8.0% (Herbert MS, 2013).

The current study evaluated pain levels during and up to one week after placement of two dental implants in the anterior mandible as measured on a VAS scale. The visual analog scale (VAS) commonly used in pain research, which has been well established as a reliable and valid research tool (Bijur PE). Factors, such as HbA1c, edema, erythema, exudate, oral pain at one week, flap closure, infection and hematoma, were evaluated with respect to if or how they affected the VAS pain score. The stepwise linear regression model found that days of pain, oral pain level at one week, edema, and HbA1c levels affected the patient's reported pain response. The oral pain level at one week was most significantly impacted with an 8mm VAS score increase for every upward shift from none, slight, moderate, to severe in edema or oral pain, and HbA1c had a 2.7mm increase in VAS score for every 1% increase.

It is an interesting finding that the pain levels could be altered by their glycemic control and warrants further research. All other outcomes including edema, erythema, exudate, oral pain at one week, flap closure, infection, and hematoma were not significantly affected by the patient's HbA1c levels. There is substantial literature demonstrating that patients with diabetes mellitus are at a higher risk for postoperative complications, such as infections, cardiovascular events and mortality with hyperglycemia being recognized as an important contributor to these serious postoperative events (Lopez LF, 2017). Similarly, infection remains a concern after implantation devices such as prosthetic joints, pacemakers, and implantable cardioverter defibrillators (Le, 2011) associated with diabetes-related immunocompromise (Abiko Y, 2010). However, it appears from the current study that our clinical protocol to manage post-operative infection, including oral antibiotics and an antimicrobial rinse may have mitigated these concerns. The inability of the current study to document the relative value of this post-operative management regimen represents another limitation of the current investigation.

In conclusion, the results of this study indicate that the post-operative healing factors; edema, erythema, exudate, oral pain at one week, flap closure, infection and hematoma, are not significantly affected by glycemic control in patients with diabetes mellitus with HbA1c levels up to 12% following dental implant placement. These findings are consistent with previous preliminary findings in regards to success and stability of dental implants in patients with diabetes type 2, reinforcing their value in consideration of the use of this therapy in this population with minimal risk to the patient. The results of this study also reveal the possibility of a significant relationship between

HbA1c and pain that is not well documented in the current literature. Finally, this study offers an important contribution to our understanding in the development of appropriate management strategies for the treatment of patients with diabetes.

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